



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-D-3049]

E8(R1) General Considerations for Clinical Studies; International Council for Harmonisation; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled “E8(R1) General Considerations for Clinical Studies.” The guidance was prepared under the auspices of the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation. The guidance describes internationally accepted principles and practices for the design and conduct of clinical studies of drug and biological products. In addition, the guidance provides an overview of the types of clinical studies that may be performed and data sources used during the product’s life cycle. The guidance is intended to promote the quality of the studies submitted to regulatory authorities, while allowing for flexibility. This guidance revises the guidance for industry “E8 General Considerations for Clinical Trials” issued in December 1997.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to

<https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-D-3049 for "E8(R1) General Considerations for Clinical Studies." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper

submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that

office in processing your requests. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-8010. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Mark Levenson, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 21, Rm. 4626, Silver Spring, MD 20993-0002, 301-796-2097, Mark.Levenson@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

Regarding the ICH: Jill Adleberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6364, Silver Spring, MD 20993-0002, 301-796-5259, Jill.Adleberg@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a final guidance for industry entitled “E8(R1) General Considerations for Clinical Studies”. The guidance was prepared under the auspices of ICH. ICH has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, high-quality medicines are developed, registered, and maintained in the most resource-efficient manner.

By harmonizing the regulatory requirements in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies,¹ standardized the reporting of important safety information, standardized marketing application submissions, and made many other improvements in the quality of global drug development and manufacturing and the products available to patients.

¹ We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

The six Founding Members of the ICH are FDA; the Pharmaceutical Research and Manufacturers of America; the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Pharmaceutical Manufacturers Association. The Standing Members of the ICH Association include Health Canada and Swissmedic. Additionally, the Membership of ICH has expanded to include other regulatory authorities and industry associations from around the world (refer to <https://www.ich.org/>).

ICH works by involving technical experts from both regulators and industry parties in detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process that results in the development of ICH guidelines. The regulators around the world are committed to consistently adopting these consensus-based guidelines, realizing the benefits for patients and for industry.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In the *Federal Register* of August 1, 2019 (84 FR 37649), FDA published a notice announcing the availability of a draft guidance entitled "E8(R1) General Considerations for Clinical Studies." The notice gave interested persons an opportunity to submit comments by September 30, 2019. After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agencies in October 2021.

This guidance finalizes the draft guidance issued on August 1, 2019. The revised final guidance describes internationally accepted principles and practices in the design and conduct of clinical studies of drug and biological products. Changes from the 2019 draft guidance to the

final guidance include a reduced emphasis on distinct phases of clinical development, the addition of examples of novel studies, and amendments to appendices. The original ICH guidance “E8 General Considerations for Clinical Trials,” that was issued in 1997 has not undergone revision previously. Since the 1997 guidance was issued, clinical trial design and conduct have become more complex, impacting the time and feasibility of developing drugs. In response, the revised guidance directly addresses study quality to ensure the protection of study participants and the generation of reliable and meaningful results, while promoting study efficiency. The ICH E8(R1) guidance focuses on the identification of factors that are critical to the study quality and the management of risks to those factors. Additionally, a wider range of study designs and data sources play an increasingly important role in drug development and are not adequately addressed in the original ICH E8 guidance. Hence, the revised final guidance addresses a broad range of study designs and data sources. The revised final guidance also provides updated cross-referencing to other relevant ICH guidances that inform the design, planning, and conduct of clinical research, without reproducing the detailed material found in those guidances.

This guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on “E8(R1) General Considerations for Clinical Studies.” It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information for investigational new drug

applications under have been approved under OMB control number 0910-0014; the collections of information for review of new drug applications in have been approved under OMB control number 0910-0001; and the collections of information for review of biologic licensing applications in have been approved under OMB control number 0910-0338.

III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.regulations.gov>, <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.

Dated: April 5, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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